Special Series

Screening for Cancer
Useful Despite Its Limitations

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Effective primary prevention strategies are currently available for only a limited number of types of malignant neoplasms. In the meantime, the most effective intervention for cancer control is screening for the early detection of cancer in otherwise asymptomatic persons. Screening is probably most useful for cancers wherein the stage at diagnosis is clearly related to curability. Early detection by screening has been shown to lead to a better outcome following the treatment of cancers of the breast, cervix, and colon. Screening for cancer also enables preneoplastic states to be detected and treated. Screening programs offer an opportunity to enhance the potential of chemoprevention. New cancer screening tests will soon be developed, including some that will detect known genetic predispositions to cancer. Each new screening test must be critically evaluated in rigorous studies before being embraced or rejected by clinicians and patients. In particular, screening efficacy must be demonstrated as judged by improved survival of those screened.

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Cancer is the second leading cause of death in the United States, accounting for almost 24% of all deaths in 1991. Each year in the United States, more than 1.25 million new cases of cancer are diagnosed and more than 540,000 people die of cancer. In addition, some 800,000 new cases of nonmelanomatous skin cancer and 120,000 cases of carcinoma in situ are diagnosed each year.[1,2]

Most cancers are thought to be due to a combination of genetic factors interacting with lifestyle factors and environmental exposures. Recent research has helped to define the molecular basis of malignant transformation and the proliferation of cells. This research suggests that mutations in DNA sequences lead to either an amplification or an increased suppression of oncogenes or to the deletion of tumor suppressor genes (or both). Oncogenes encode for cellular growth factor receptors, growth factors, or other elements of the proliferative mechanisms. Tumor suppressor genes encode for regulatory proteins that normally suppress cellular proliferation. A genetic susceptibility to cancer results from mutations that alter normal cellular regulatory processes. Such mutations may be due to exposure to environmental influences such as ionizing radiation or ultraviolet light, to infectious agents such as the human papillomavirus or the Epstein-Barr virus, or to other unknown factors.

As with most other diseases, preventing cancer has the potential to save more lives than does treating it. The primary prevention of cancer includes measures to reduce or remove risk factors (counseling about stopping or not starting cigarette smoking to prevent lung cancer) or chemoprevention to interfere with the multistage carcinogenic process (administering isotretinoin to prevent oral cancer). Secondary prevention entails screening techniques designed to promote the early detection of disease or precursor states (routine Papanicolaou screening to detect invasive cervical cancer or cervical intraepithelial neoplasia). Tertiary prevention measures aim to limit the effects of established disease (partial mastectomy and radiation therapy to remove and control localized breast cancer).

Primary prevention strategies are the most effective and economical of all methods of cancer control. Effective strategies include risk-factor modification such as stopping, moderating, or avoiding tobacco use, alcohol consumption, and exposure to ultraviolet light or industrial carcinogens; measures to prevent viral transmission such as the use of condoms and barrier contraception methods; dietary changes to decrease fat intake and increase fiber intake; and various chemoprevention regimens. Chemopreventive agents under investigation include vitamins and vitamin derivatives such as

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isotretinoin, prostaglandin inhibitors such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), and hormone-suppressing agents such as tamoxifen citrate and finasteride.[2,3]

In the long run, primary prevention strategies have a greater effect than secondary prevention (screening). The National Cancer Institute estimates that even a 30% reduction in tobacco consumption would yield a 10% reduction in the number of cancer deaths, whereas widespread screening for breast and cervical cancer would yield only a 3% reduction. Unfortunately, given our limited knowledge about the causes of cancer, effective primary prevention strategies are currently available for only a limited number of types of malignant diseases.

In the meantime, the most effective intervention for cancer control is screening for the early detection of cancer in otherwise asymptomatic persons. Such detection may be achieved through simple observation (skin or oral examinations), palpation (breast or testicular examinations), or laboratory tests and procedures (Pap smear, sigmoidoscopy, or mammography).

Cancer screening tests ideally should be measured against several criteria before widespread adoption. First, the population to be screened must have a sufficiently high prevalence of the cancer, and affected persons must be likely to comply with subsequent tests and treatments. Second, the cancer must have sufficient morbidity and mortality, effective and acceptable treatment must be available for it, a presymptomatic period must exist during which it is detectable, and its early detection and treatment must yield better results than otherwise. Finally, the test must be able to detect early cancer with sufficient sensitivity and specificity, at low cost and risk, and there must be confirmatory tests that are both practicable and available.

Screening is not useful if no method of early detection exists (cancer of the pancreas) or if there is no apparent localized stage (leukemia). Screening is not useful if it cannot be shown that early detection has an effect on mortality rates. Several randomized, controlled trials of chest radiograph and sputum cytologic screening for lung cancer failed to show a beneficial effect on mortality rates for this common cancer. Screening for ovarian cancer with pelvic examinations, serum markers (CA 125), and transvaginal ultrasonography has not been shown to decrease its mortality rate. For the same reason, there is currently controversy about the usefulness of screening for prostate cancer by digital rectal examination, serum prostate-specific antigen levels, or transrectal ultrasonography.[4]

Early detection by screening has led to an improvement in outcome following the treatment of cancers of the breast, cervix, and colon. For each, efficacy studies have reported findings from asymptomatic persons in the general population.

For breast cancer, convincing evidence exists that regular clinical breast examinations and mammography for women 50 to 69 years of age are effective in reducing mortality from this disease. In the mid-1970s, for example, the Swedish National Board of Health sponsored a trial in which 134,867 women aged 40 and older were randomly assigned to receive either one-view mammography at age-dependent intervals (24 to 33 months) or routine care. At five-year follow-up, the overall breast cancer mortality was 31% lower in the group offered screening, and the estimated relative risk for death from breast cancer among women aged 50 to 74 was 0.61 (95% confidence interval [CI], 0.44 to 0.84).[5] Many other well-conducted controlled trials and case-control studies have varied the number of mammographic views taken, the frequency of mammography, and the duration of screening. All but one of the randomized trials and most of the case-control series have shown clinically—and in most cases statistically—significant reductions in breast cancer mortality among women screened.[6,7] Recently a 5% decrease in breast cancer mortality has been shown among white women in the United States, but not among black women (who generally have lower mammography screening rates). Controversy still exists regarding the use of screening mammography in women aged 40 to 49 and in those older than 70.

Although randomized, controlled trials are not available, many studies have shown that regular screening by Pap tests can decrease the cervical cancer mortality rate in women who are sexually active or aged 18 years or older. In Iceland, for example, the establishment of a comprehensive, centralized cervical cytologic screening program led to a notable increase in the number of cases of severe dysplasia and carcinoma in situ treated, a twofold reduction in the mortality of invasive cervical cancer, and a notable decrease in the incidence of advanced-stage tumors.[8] In the United States, the death rate from cervical cancer decreased by more than 70% between 1950 and 1985 with increasing use of the Pap test. Many studies have found a relationship between Pap test screening intensity and changes in cervical cancer mortality rates over time, and a host of cohort and case-control studies have confirmed its usefulness.[6,7] Although most physicians and patients accept its value, controversy still exists regarding the optimal frequency of Pap smear screening in various segments of the population.

Regular screening sigmoidoscopy in persons older than 50 years appears to reduce the mortality from colon cancer. A careful case-control study of rigid sigmoidoscopy found a 59% reduction in colorectal cancer mortality; the risk of colon cancer death was reduced as much as ten years after a single examination.[9] Here again, controversy continues regarding the age at which to begin and the interval between screening sigmoidoscopies.

For most cancers, standardized staging to estimate the apparent extent of disease at the time of diagnosis is extremely valuable, both for planning treatment and for determining prognosis. In the United States, the American Joint Committee on Cancer's TNM staging system is the most widely used system. It is based on a model that postulates that the untreated primary tumor (T) will gradually increase in size, leading to local invasion, then a spread to regional lymph nodes (N) and, eventually, to distant

metastases (M).[2] Unfortunately, the TNM and other staging systems do not always accurately predict prognosis. For many cancers, the primary tumor is not clinically evident until local invasion or involvement of regional lymph nodes has already occurred. For others, the clinical stage at the time of diagnosis does not take into account variations in tumor biology or aggressiveness. For certain of these tumors, specific pathologic characteristics can be helpful in more accurately defining the prognosis (estrogen and progesterone receptors or proliferative index for breast cancer; histologic grade for sarcoma).

Screening is probably most useful for cancers whose stage at diagnosis is clearly related to curability, that is, for cancers with the highest cure rates reported when the tumor is small and there is no evidence of metastasis. For instance, with breast cancer, the expected five-year survival rate is 85% for patients who are in stage I and 60% to 70% for those in stage II, but only 30% to 55% in stage III and 5% to 10% in stage IV. With colon cancer, the five-year survival rates are 80% to 100% for stage I, 50% to 75% for stage II, 30% to 50% for stage III, and 5% for stage IV disease. With cervical cancer, the five-year survival rate is virtually 100% for carcinoma in situ (cervical intraepithelial neoplasia type III), but decreases to 88%, 51%, and 14% for detection at localized, regional, and distant invasive stages, respectively.[7]

For other cancers, such as small-cell carcinoma of the lung, distant metastases have already occurred, often before the small primary tumor can be detected. Obviously, screening for such cancers is not useful. Screening for other cancers in normal asymptomatic persons, even in "high-risk" segments of the population, is not currently recommended, usually because available screening tests do not meet all of the criteria mentioned earlier.

New cancer screening tests will soon be developed. Each new screening test must be critically evaluated in rigorous studies before being embraced or rejected by clinicians and patients. In particular, screening efficacy must be demonstrated as judged by enhanced survival of screened persons. Studies must also be carefully designed to avoid length- and lead-time biases.

Screening for cancer offers clinicians and patients at least three other benefits. First, such screening enables the detection and treatment of preneoplastic states. In fact, screening examinations usually discover many more precursor states than established cancers. In the United States, cervical Pap smear screening currently leads to the discovery of cervical intraepithelial neoplasia—dysplasia and carcinoma in situ—much more often than invasive cancer. (In 1995, it is estimated that 65,000 new cases of carcinoma in situ of the uterine cervix will occur versus 15,800 new cases of invasive cervical carcinoma.[1]) Sigmoidoscopic screening of asymptomatic persons enables the detection of many more persons with adenomatous polyps—approximately 50 to 100 per 1,000 examinations—than cancers: about 1 to 4 per 1,000 examinations. (Autopsy studies have shown that as many as 10% to 33% of older adults have colonic polyps at death, but only 2% to 3% have colorectal cancer.[7]) The detection of cervical dysplasia enables cervical conization or, in experienced hands, cryotherapy or laser ablation and presumably prevents a progression to carcinoma in situ and invasive cancer. For those discovered to have adenomatous colonic polyps, colonoscopic polypectomy can be undertaken; such therapy appears to reduce the risk of subsequent colon cancer by 90%.[10] In addition, chemoprevention with aspirin and other NSAIDs may be undertaken.[2,3] Using this rationale, screening for preneoplastic lesions of the oral cavity (for leukoplakia) and skin (for dysplastic nevi) has been recommended by some authorities, at least for high-risk persons—those who smoke or who have a family history of melanoma. Further studies are needed of the effect of such screening strategies on the mortality of these cancers.

Second, chemoprevention of cancer is a new and exciting area of cancer control. Screening programs offer an opportunity to enhance its potential. Chemoprevention strategies can be applied to four groups: patients who have previously had cancer (to prevent second cancers); those with preneoplastic lesions; those who are at high risk for neoplasia, whether because of family history, lifestyle, or occupation; and other asymptomatic persons in the general population.[2] Logically, chemoprevention will prove most useful to patients in the second and third groups. Screening can enable a clinician to differentiate patients who are members of these groups and thus to prescribe chemopreventive agents most appropriately.

Finally, new screening approaches will soon be developed to detect known genetic predispositions to cancer. Hereditary predispositions to certain forms of cancer have now been linked to specific molecular events within specific genes. Consider colon cancer, for example. Researchers have recently identified the abnormal gene (adenomatous polyposis coli; *APC*) on chromosome 5 that is responsible for the syndrome of familial adenomatous polyposis. The *APC* gene has been cloned, and the protein it encodes has been characterized. Germline mutations in the *APC* gene resulting in reduced expression or truncated proteins have been identified in more than 90% of families with familial adenomatous polyposis. Researchers have also demonstrated mutations in the *APC* gene in patients with sporadic (nonfamilial) adenomatous polyps and in patients with colon cancer. In addition, the genetic abnormalities in the hereditary nonpolyposis colon cancer syndrome have been located using linkage analysis of large kindreds to specific regions of chromosomes 2, 3, and 7. In recent months, four genes at these sites have been identified and cloned: *hMSH2* and *hPMS1* on chromosome 2, *hMLH1* on chromosome 3, and *hPMS2* on chromosome 7.[11] More than 90% of patients with the hereditary syndrome of nonpolyposis colon cancer have mutations in one of these genes, which appear to have a central role in identifying and repairing sites of DNA base-pair mismatch that may occur during normal DNA replication. Malfunctioning of these "genetic proofreaders" presumably means that errors can accumulate during repeated cell divisions, eventually resulting in malignant transformation.

An important consequence of these discoveries is that it is now possible to use linked genetic markers to identify affected family members of cancer patients and to offer them appropriate preventive measures. For example, polymerase chain reaction techniques can be used to analyze DNA from desquamated colonic epithelial cells in stool for mutant alleles predisposing to colon cancer.[12] Although a number of important questions must be addressed before recommending widespread DNA testing for presymptomatic identification of cancer risk,[13] such techniques may enable more targeted cancer screening of high-risk persons. Such targeted screening may lead to earlier chemoprevention, the detection of lesions, and surgical or other therapeutic intervention, enhancing the possible reduction of cancer mortality rates.

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